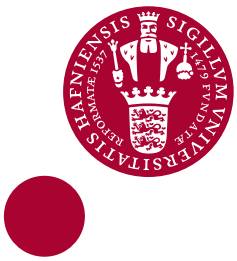

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Progressive Decline in Estimated Glomerular Filtration Rate in Patients With Diabetes After Moderate Loss in Kidney Function—Even Without Albuminuria

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Persons with diabetes but no chronic kidney disease (CKD) and without albuminuria have the same age-related decline in kidney function as the background population. Whether this also applies following moderate loss in kidney function is unknown. We quantified the impact of albuminuria status on the development of estimated glomerular filtration rate (eGFR) trajectories following CKD stage 3 (CKD3) and assessed potential heterogeneous development patterns among the subgroup with normoalbuminuria.

RESEARCH DESIGN AND METHODS

We used repeated clinical measures during up to 16 years of follow-up in 935 persons with type 1 diabetes and 1,984 with type 2 diabetes. Trajectories of eGFR by diabetes type and albuminuria status following CKD3 were estimated with spline mixed-effects models with adjustment for relevant confounders. Latent class trajectory modeling was used to find distinct patterns of eGFR development in the subgroups with normoalbuminuria.

RESULTS

Mean annual declines in eGFR for normo-, micro- and macroalbuminuria the first 10 years following CKD3 were 1.9, 2.3, and 3.3 mL/min/1.73 m^2 in type 1 diabetes and 1.9, 2.1, and 3.0 in type 2 diabetes, respectively. For normoalbuminuria, two distinct eGFR patterns were found, one with accelerated declining eGFR levels. This specific progression pattern was associated with less use of lipid-lowering treatment, renin-angiotensin system blockers, and other antihypertensive treatment.

CONCLUSIONS

Our results support a diabetes-dependent decline in kidney function without albuminuria following CKD3, with a subgroup showing a progressive decline. Furthermore, this group seems to be undertreated in terms of cardioprotective and renal protective treatment and suggests that increased attention should be drawn to normoalbuminuric diabetic kidney disease.

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Chronic kidney disease (CKD) is affecting approximately 10% of the global population (1), with diabetes as the leading risk factor for renal impairment. CKD is usually progressive and may lead to end-stage kidney disease (ESKD), also known as kidney failure.

General improvements in medical care have reduced the prevalence of diabetes-related complications such as myocardial infarction and stroke. However, despite intensified treatment of hypertension and increased use of renin-angiotensin system (RAS) blockers, the frequency of ESKD in diabetes remain virtually unchanged (2). With the growing number of people with diabetes, this could have a massive effect on the number of cases of ESKD.

Diabetic kidney disease is silent until the very late stages. Moderate to severe stages of CKD are measured by the estimated glomerular filtration rate (eGFR) (3), and studies have shown that already from CKD stage 3 (CKD3), corresponding to eGFR $<$60 mL/min/1.73 m^2, risk of cardiovascular disease and mortality is increased (4).

Another marker of kidney damage is albuminuria, and it is a common assumption that in persons with diabetes, a decline in kidney function is preceded by albuminuria. However, a substantial number of persons entering CKD3 will have normoalbuminuria (3,5,6) and, especially in type 2 diabetes, the prevalence of this stage (CKD3 with normoalbuminuria) is increasing (6). It is debated whether eGFR development in CKD3 with normoalbuminuria reflects normal age-related decline in renal function, diabetic kidney disease with previous albuminuria normalized by antihypertensive treatment, or a new phenotype of kidney disease in diabetes. A better understanding of disease progression in this group of people is imperative for optimal risk stratification and subsequent clinical treatment.

A linear decline in eGFR over time is often assumed (7), but while this may be true in some groups of persons with diabetes, others have nonlinear patterns of development (8,9). For the ability to detect true nonlinear development patterns, multiple repetitive measurements of eGFRs over longer periods of time are needed.

The aim of this study was to assess the impact of albuminuria status on the development over time in eGFR in a large population of people with diabetes entering CKD3 and with multiple subsequent clinical visits over a long period of follow-up. Furthermore, we aimed to study the shape of the eGFR curve with a specific aim of assessing potential heterogeneity in eGFR development among persons with diabetes and normoalbuminuria after entering CKD3.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The study is based on 3,343 adults with type 1 diabetes or type 2 diabetes treated at Steno Diabetes Center Copenhagen in the period 1 January 2001 to 31 May 2017 with at least one measurement of an eGFR in CKD3 (eGFR $<$60 mL/min/1.73 m^2). Clinical examinations prior to the first recorded low eGFR measurement in CKD3 were not considered. We excluded persons with no or with an implausible date of diabetes diagnosis (n = 40 [1.1%]). Another 384 (11.5%) persons were excluded due to no measurements of serum creatinine following their first low eGFR measurement, leaving 2,919 persons with diabetes with a total of 28,387 clinical measurements for analysis.

According to Danish law, ethics approval and patient consent are not required for registry-based studies. Access to and use of the described data are approved by the Danish Data Protection Agency.

Measurements and Definitions

For separation of type 1 from type 2 diabetes, type 1 diabetes was clinically diagnosed based on phenotype and in accordance with the Danish National Diabetes Quality Database requirements as previously described (10).

Because date of diabetes diagnosis is only recorded as year of diagnosis, we set the date to 1 July of that year. However, if the person had a clinical measurement of serum creatinine before 1 July that year, the date of diabetes diagnosis was changed to the date of the clinical measurement.

Urinary albumin excretion ratio was measured in 24-h sterile urine collections or from the urinary albumin-to-creatinine ratio (UACR) measured on a single first-void urine sample. Urine creatinine, urine albumin, and serum creatinine concentrations were determined by an enzymatic method (Hitachi 912 system). During 2010, the study laboratory gradually implemented the Vitros 5600 Integrated System (Ortho Clinical Diagnostics, Illkirch Cedex, France). All Vitros values were converted to correspond with Hitachi values. Albuminuria status was classified as normoalbuminuria (UACR $<$30 mg/g), microalbuminuria (30–299 mg/g), or macroalbuminuria ($\geq$300 mg/g).

The Chronic Kidney Disease Epidemiology Collaboration standard equation (11) was used to calculate eGFR, as recommended in the 2013 guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) foundation. CKD3 was defined as eGFR $<$60 mL/min/1.73 m^2 according to guidelines (3).

Brachial systolic and diastolic blood pressure was measured twice with an automated oscillometric blood pressure recorder, and the average of the measurements was used. For persons with possible white-coat hypertension, home blood pressure monitoring was offered according to guidelines (12). HbA_{1c} was determined by standard high-performance liquid chromatography (normal range 4.1–6.4% [21–46 mmol/mol]) (Variant; Bio-Rad Laboratories, Munich, Germany). Total cholesterol, HDL cholesterol, and triglycerides were measured by using the Hitachi 912 system (Roche Diagnostics, Mannheim, Germany). LDL cholesterol was calculated by using the Friedewald equation (13).

Smoking was defined as current smoker (yes/no). RAS blockers were defined as any use of ACE inhibitors or angiotensin II receptor blockers (yes/no). Retinopathy status was assessed from retinal photographs taken through dilated pupils. Grading was based on the worse eye and classified according to the international clinical diabetic retinopathy severity scale into three groups as follows: no apparent retinopathy, mild/moderate retinopathy, or severe retinopathy (14).

Statistical Analysis

Persons with diabetes were followed from their first recorded low eGFR ($<$60 mL/min/1.73 m^2) (baseline) until their last clinical examination. Trajectories of eGFR development over time after baseline were estimated by mixed-effects models with a person-specific random intercept and slope. The models were fitted using the lmer function, and 95% CIs for the mean curves were calculated with bootstrapping (1,000 repeats) using the bootMer function in

the lme4 package (15). We used a two-step approach for confounder adjustment, first adjusting for the nonmodifiable factors sex, age at diabetes diagnosis, diabetes duration, and calendar time (model 1) and then additionally adjusting for use of RAS blockers, retinopathy status, HbA_{1c}, antihypertensive treatment, blood pressure, current smoking, and lipid-lowering treatment (model 2). Interaction between time and albuminuria status was included and tested in model 1. We further tested for nonlinearity in the eGFR development by comparing a model with a linear term for time with a model using natural cubic splines to model the association with time. For the spline model, knots were set at the quartiles of the time distribution. In model 2, interaction between time and use of RAS blockers was tested. Except for sex and age at diagnosis, all factors were included as time-varying covariates, e.g., a person with normoalbuminuria at baseline who subsequently progresses to microalbuminuria will contribute with eGFR measurements first in the normoalbuminuric group and later in the microalbuminuric group. Prior to analysis, eGFR was log transformed to fulfill the assumption of normally distributed model residuals. The analysis was stratified by diabetes type.

Because a clinical classification of moderate loss of kidney function (CKD3) may result in intensified treatment, we repeated the analysis following persons from an eGFR $<$70 mL/min/1.73 m^2. A total of 978 persons with type 1 and 2,098 with type 2 diabetes were included in this sensitivity analysis.

In the subset of persons with normoalbuminuria who were also without albuminuria at baseline, we further investigated heterogeneity in the eGFR trajectories, using latent class trajectory modeling (LCTM) (16). LCTM is a data-driven hypothesis-free statistical approach for identifying clusters of distinct developmental patterns of a longitudinal measured marker. We adjusted for calendar time and modeled time since baseline with natural cubic splines including a person-specific random intercept and slope. The models were fitted using the hlme function in the R package lcmm (17). The optimal number of latent classes was determined using the Bayesian information criterion (smaller is better), relative entropy, mean posterior probability of class membership, group size of the trajectories, and interpretability (18). Solutions with two, three, four, and five latent classes were tested. The analysis was based on 397 with type 1 and 857 with type 2 diabetes and stratified by diabetes type.

Statistical analyses were performed in R, version 3.4.1 (http://www.r-project.org/).

RESULTS

The study population comprised 935 persons with type 1 diabetes with 10,110 clinical measurements with a median follow-up time of 5.1 years (interquartile limits 2.3; 9.0) and 1,984 with type 2 diabetes with 18,277 clinical measurements followed for 3.7 years (1.0; 6.8).

In comparison with type 1 diabetes, persons with type 2 diabetes were on average 10 years older and more often of male sex and were three times as likely to be without any apparent retinopathy at baseline (39% vs. 13%). For both type 1 and type 2 diabetes, close to half of the study participants had normoalbuminuria at baseline, which was associated with a more favorable lipid profile, lower levels of blood pressure and HbA_{1c}, and a higher age at diabetes diagnosis in comparison with those with micro- or macroalbuminuria (Tables 1 and 2). The degree of antihypertensive treatment was comparable across groups of albuminuria status. However, having normoalbuminuria was associated with less frequent use of RAS blockers—but with more frequent use of lipid-lowering medication. Difference in treatment across albuminuria status was especially pronounced in type 1 diabetes. In people with type 1 diabetes, we also found a higher relative difference in the proportion without any retinopathy between the normo- and macroalbuminuria group (20% vs. 4%) compared with the group with type 2 diabetes (46% vs. 25%).

In the repeated longitudinal analysis, we found for both type 1 and type 2 diabetes a significantly better fit with the spline model compared with the model including only a linear trend in eGFR over time ($P < 0.001$). Therefore, time was modeled using natural cubic splines with knots set at 1, 3, and 6 years for type 1 diabetes and at 1, 2, and 5 years for type 2 diabetes. Albuminuria status significantly modified the development in eGFR ($P < 0.001$) in both types of diabetes, with the steepest decline in kidney function among persons with macroalbuminuria (Fig. 1). We found no modifying effect of RAS blockers on the eGFR development over time in any types of diabetes ($P \geq 0.060$). Because estimated eGFR trajectories were similar for models 1 and 2 (Supplementary Fig. 1), only curves for model 2 are shown. The estimated average annual decline in eGFR for normo-, micro-, and macroalbuminuria the first 10 years following CKD3 was 1.9, 2.2, and 3.3 mL/min/1.73 m^2 in type 1 diabetes and 1.9, 2.1, and 2.9 mL/min/1.73 m^2 in type 2 diabetes (Supplementary Table 1). In persons with normoalbuminuria, the first recorded low eGFR was followed by 1 year of increasing eGFR of 1.6 mL/min/1.73 m^2 in both type 1 and type 2 diabetes before eGFR again declined at an approximately linear rate. Among persons with microalbuminuria, there was a similar period of stable eGFR before an approximately linear rate of decline in eGFR occurred (Fig. 1).

In the sensitivity analysis following persons from an eGFR $<$70 mL/min/1.73 m^2, the trajectories were overall similar in shape to those in Fig. 1 but without a short-term increase in eGFR (Supplementary Fig. 2).

From the LCTM approach among persons with normoalbuminuria who were also without albuminuria at baseline, the two-class solutions were chosen for both types of diabetes (for details on results for 3-, 4-, or 5-class solutions see Supplementary Tables 2 and 3 and Supplementary Figs. 3 and 4). The two distinct patterns of eGFR development in type 1 and type 2 diabetes are shown in Fig. 2.

For type 1 diabetes, the majority (class 1 [86%]) followed a pattern of eGFR characterized by an initial increase and then a steady linear decline. The second and smaller class (class 2 [14%]) had a steep decline in eGFR levels the first 4 years after entering CKD3, which seemed to level off thereafter. At baseline, class 2 had on average lower eGFR values and a worse lipid profile and were less likely in lipid-lowering treatment. Members of class 1 were three times as likely to be without any apparent retinopathy (Table 3).

For type 2 diabetes, the majority (class 1 [90%]) followed a pattern of eGFR characterized by an initial increase and then a steady linear decline, resembling that of the large class among type 1

Table 1—Characteristics of the study population with type 1 diabetes in total and by albuminuria status at baseline

		Albuminuria status		
	Total	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
N	935	427	264	244
No. of clinical measurements	8 (4; 14)	7 (4; 12)	9 (5.0; 15.5)	10 (4; 18)
Follow-up time (years)	5.1 (2.3; 9.0)	5.2 (2.6; 9.0)	5.0 (2.5; 8.9)	5.1 (2.1; 9.0)
Age (years)	59.2 (14.5)	65.0 (12.5)	59.5 (13.4)	48.9 (13.2)
Male sex (%)	48.9 (45.6; 52.1)	37.2 (32.6; 42)	53.8 (47.6; 59.9)	63.9 (57.6; 70.0)
Age at diabetes diagnosis (years)	24.5 (12.1; 38.7)	31.0 (15.7; 45.8)	23.2 (11.8; 37.0)	14.5 (8.2; 27.8)
Diabetes duration (years)	31.7 (22.8; 41.3)	32.2 (22.6; 42.8)	34.6 (24.4; 42.6)	29.2 (22.6; 37)
HbA_{1c} (%)	8.8 (1.4)	8.5 (1.3)	8.8 (1.4)	9.2 (1.5)
HbA_{1c} (mmol/mol)	72.2 (15.4)	68.9 (13.9)	73.1 (15.2)	77.1 (16.6)
BMI (kg/m^2)	25.3 (4.3)	25.4 (4.6)	25.1 (3.8)	25.4 (4.2)
eGFR ($mL/min/1.73\ m^2$)	53.3 (45.5; 57.1)	54.6 (48.4; 57.7)	53.0 (45.0; 57.0)	50.6 (36.2; 55.8)
UACR (mg/g)	45.5 (11.0; 334.0)	9.5 (5.0; 18.0)	89.0 (42.0; 209.0)	1,080 (487; 2,315)
Potassium (mmol/L)	4.3 (0.5)	4.3 (0.5)	4.4 (0.5)	4.3 (0.6)
Sodium (mmol/L)	138.0 (3.6)	138.4 (3.3)	137.6 (3.8)	137.7 (3.6)
Systolic blood pressure (mmHg)	139.8 (21.0)	137.8 (20.0)	138.6 (22.5)	144.6 (20.3)
Diastolic blood pressure (mmHg)	75.0 (11.3)	72.8 (10.3)	74.0 (11.3)	80.3 (11.4)
Total cholesterol (mmol/L)	5.1 (1.2)	5.1 (1.1)	4.9 (1.1)	5.5 (1.3)
HDL cholesterol (mmol/L)	1.7 (0.6)	1.8 (0.6)	1.7 (0.6)	1.6 (0.6)
LDL cholesterol (mmol/L)	2.7 (0.9)	2.7 (0.9)	2.5 (0.9)	3.1 (1.0)
Triglycerides (mmol/L)	1.2 (0.9; 1.8)	1.1 (0.8; 1.6)	1.2 (0.9; 1.8)	1.5 (1.0; 2.2)
RAS blockers (%)	62.8 (59.6; 65.9)	59.5 (54.7; 64.2)	62.1 (56.0; 68.0)	69.3 (63.1; 75.0)
Antihypertensive treatment (%)	79.8 (77.1; 82.3)	78.0 (73.8; 81.8)	81.1 (75.8; 85.6)	81.6 (76.1; 86.2)
Lipid-lowering medication (%)	43.7 (40.5; 47)	46.4 (41.6; 51.2)	45.8 (39.7; 52.1)	36.9 (30.8; 43.3)
Retinopathy status (%)				
No apparent retinopathy	13.0 (10.7; 15.7)	20.0 (16.0; 24.5)	9.0 (5.5; 13.8)	3.9 (1.6; 7.8)
Mild/moderate retinopathy	22.8 (19.9; 26.0)	28.7 (24.1; 33.7)	22.9 (17.4; 29.1)	11.1 (6.9; 16.6)
Severe retinopathy	64.2 (60.6; 67.6)	51.3 (45.9; 56.6)	68.1 (61.3; 74.3)	85.0 (78.9; 89.9)
Smoking (%)				
No	55.4 (51.3; 59.5)	62.2 (56.5; 67.6)	53.3 (45.4; 61.0)	40.4 (31.3; 49.9)
Previous	2.7 (1.6; 4.4)	3.3 (1.6; 6.0)	1.8 (0.4; 5.2)	2.6 (0.5; 7.5)
Yes	41.9 (37.8; 46.0)	34.5 (29.2; 40.2)	44.9 (37.2; 52.8)	57.0 (47.4; 66.3)
Alcohol intake (units/week)*				
0	14.0 (11.2; 17.1)	12.0 (8.5; 16.2)	13.1 (8.3; 19.4)	20.5 (13.5; 29.2)
1–20	75.0 (71.2; 78.5)	80.0 (75; 84.4)	71.3 (63.6; 78.1)	67.0 (57.4; 75.6)
>20	11.0 (8.6; 13.9)	8.0 (5.2; 11.7)	15.6 (10.4; 22.2)	12.5 (7.0; 20.1)
Regular exercise (%)†	57.7 (53.5; 61.7)	62.7 (56.9; 68.2)	50.9 (42.9; 58.9)	54.0 (44.4; 63.4)

Data are mean (SD), median (interquartile limits), or proportion (95% CI). *A unit of alcohol: 12 g pure alcohol. †Regular exercise: ≥30 min per day.

diabetes. The second and smaller class (class 2 [10%]) had a steep decline in eGFR the first 3 years after entering CKD3 and then a slight increase in eGFR. However, the median follow-up time in class 2 was only 2 years, which was half of that in class 1. Furthermore, at the time of the first eGFR measurement in CKD3, those in class 2 were on average older with a lower eGFR value but a better blood pressure profile and with less antihypertensive treatment. The lipid profile was similar between the two classes despite class 2 receiving less lipid-lowering treatment and engaging in less regular exercise. Persons in class 2 were less likely to use RAS blockers. There was no difference in retinopathy status, and in both classes nearly half were without any apparent retinopathy (Table 3).

CONCLUSIONS

For both types of diabetes, we found eGFR levels to be on a progressive declining trajectory when persons enter CKD3. This was also true for persons with normoalbuminuria, although with a less steep decline in eGFR compared with micro- and macroalbuminuria.

The estimated eGFR trajectories were generally following a linear pattern, which for the normoalbuminuric group was true after an initial increase in eGFR. Our findings were similar for type 1 and type 2 diabetes. Previous studies have shown diverging results on the linearity of eGFR development. A previous analysis of the African American Study of Kidney Disease and Hypertension (AASK) trial found that almost 42% of the eGFR trajectories were nonlinear, but this was not a study exclusively including persons with diabetes (8). Studies among persons with diabetes or stratified by diabetes status show a lower probability of nonlinear eGFR trajectories (7,9,19). Our study was additionally stratified both by diabetes type and by albuminuria status and further adjusted for various time-varying confounders. This may have reduced the heterogeneity to a degree to

Table 2—Characteristics of the study population with type 2 diabetes in total and by albuminuria status at baseline

		Albuminuria status		
	Total	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
N	1,984	942	664	378
No. of clinical measurements	7 (3; 12)	6 (3; 10)	7 (4; 13)	7 (3; 14)
Follow-up time (years)	3.7 (1.0; 6.8)	3.6 (0.9; 6.6)	4.3 (1.3; 7.4)	3.2 (1.0; 6.4)
Age (years)	69.3 (9.3)	70.5 (8.5)	69.5 (9.3)	66.1 (10.5)
Males (%)	57.6 (55.3; 59.7)	47.7 (44.5; 51)	64.0 (60.2; 67.7)	70.7 (65.8; 75.2)
Age at diabetes diagnosis (years)	55.7 (47.4; 63.4)	57.4 (49.9; 64.7)	55.3 (47.2; 63.3)	51.3 (43.7; 59.6)
Diabetes duration (years)	13.4 (7.8; 19.3)	12.8 (7.6; 18.9)	13.6 (7.8; 19.7)	14.5 (8.7; 19.6)
HbA_{1c} (%)	8.2 (1.6)	8.1 (1.6)	8.3 (1.7)	8.6 (1.7)
HbA_{1c} (mmol/mol)	66.5 (17.8)	64.6 (17)	67.4 (18.3)	70.0 (18.3)
BMI (kg/m^2)	30.5 (5.7)	30.4 (5.6)	30.5 (5.7)	30.7 (5.7)
eGFR ($mL/min/1.73\ m^2$)	52.4 (43.9; 57.1)	53.5 (45.5; 57.4)	51.7 (43.8; 57.1)	50.7 (38.5; 56.5)
UACR (mg/g)	34.5 (9.0; 176.0)	9.0 (5.0; 17.0)	87.0 (46.5; 165.0)	779.5 (404; 1,670)
Potassium (mmol/L)	4.3 (0.5)	4.3 (0.5)	4.3 (0.5)	4.3 (0.5)
Sodium (mmol/L)	139.0 (3.5)	139.2 (3.5)	139.0 (3.6)	138.8 (3.4)
Systolic blood pressure (mmHg)	141.3 (22.3)	136.8 (21.0)	141.7 (21.5)	151.6 (23.7)
Diastolic blood pressure (mmHg)	75.4 (11.8)	73.8 (11.2)	75.7 (11.7)	79.2 (12.6)
Total cholesterol (mmol/L)	4.7 (1.3)	4.6 (1.2)	4.6 (1.2)	5.1 (1.5)
HDL cholesterol (mmol/L)	1.2 (0.4)	1.3 (0.4)	1.2 (0.4)	1.2 (0.4)
LDL cholesterol (mmol/L)	2.5 (1.1)	2.4 (1.0)	2.4 (1.0)	2.8 (1.3)
Triglycerides (mmol/L)	1.9 (1.4; 2.9)	1.8 (1.3; 2.7)	2.0 (1.4; 3.0)	2.2 (1.6; 3.2)
RAS blockers (%)	55.2 (53.0; 57.4)	52.4 (49.1; 55.6)	58.9 (55.0; 62.7)	55.7 (50.5; 60.7)
Antihypertensive treatment (%)	72.1 (70.1; 74.1)	70.2 (67.2; 73.1)	75.6 (72.2; 78.8)	70.7 (65.8; 75.2)
Lipid-lowering medication (%)	50.6 (48.4; 52.8)	51.5 (48.3; 54.8)	50.9 (47.0; 54.8)	47.8 (42.6; 52.9)
Retinopathy status (%)				
No apparent retinopathy	38.6 (36.2; 40.9)	46.4 (42.9; 49.9)	34.9 (30.9; 39.0)	25.2 (20.5; 30.4)
Mild/moderate retinopathy	25.1 (23.0; 27.2)	24.9 (22.0; 28.1)	27.8 (24.1; 31.7)	20.4 (16.1; 25.3)
Severe retinopathy	36.4 (34.1; 38.7)	28.7 (25.6; 31.9)	37.3 (33.3; 41.5)	54.3 (48.6; 59.9)
Smoking (%)				
No	61.5 (58.8; 64.1)	65.4 (61.7; 69.0)	60.5 (55.8; 65.1)	51.4 (44.6; 58.1)
Previous	4.5 (3.5; 5.8)	3.3 (2.1; 5.0)	6.1 (4.1; 8.7)	5.0 (2.5; 8.7)
Yes	34.0 (31.5; 36.6)	31.3 (27.8; 34.9)	33.4 (29.0; 38.0)	43.7 (37.1; 50.5)
Alcohol intake (units/week)*				
0	21.4 (19.2; 23.7)	19.6 (16.6; 22.7)	22.1 (18.3; 26.3)	25.6 (19.9; 32)
1–20	71.5 (69.0; 73.9)	74.7 (71.3; 77.9)	68.7 (64.1; 73.0)	67.0 (60.3; 73.2)
>20	7.1 (5.8; 8.7)	5.7 (4.1; 7.8)	9.2 (6.7; 12.3)	7.4 (4.3; 11.8)
Regular exercise (%)†	42.2 (39.6; 45.0)	43.8 (40.1; 47.7)	41.4 (36.7; 46.2)	38.8 (32.2; 45.7)

Data are mean (SD), median (interquartile limits), or proportion (95% CI). *A unit of alcohol: 12 g pure alcohol. †Regular exercise: ≥30 min per day.

which the mean estimated eGFR trajectories were overall linear.

However, we did find some degree of heterogeneity in eGFR development among persons with normoalbuminuria and CKD3, with most persons showing an initial improvement in kidney function before further decline in eGFR. This short-term increase in eGFR is in line with two recent studies in an Indigenous Australian population at high risk of CKD (20) and in a Chinese population with type 2 diabetes (21) and may be a consequence of intensified treatment following a clinical classification of moderate loss of kidney function. We found no short-term improvement in eGFR in the sensitivity analysis following persons from an eGFR <70 mL/min/1.73 m^2, which in itself does not indicate loss of kidney function (Supplementary Fig. 2). We therefore believe the short-term increase in eGFR among persons with normoalbuminuria and CKD3 in our study to be a treatment effect rather than a regression-to-the-mean phenomenon.

Among persons with diabetes with CKD3 and normoalbuminuria, it appears that the observed decline in eGFR in the first 3–4 years following baseline to a large extent is driven by a small group with accelerated declining eGFR levels. This specific progression pattern was associated with less use of lipid-lowering treatment, RAS blocking, and other antihypertensive treatment. Although interpretation of such observational data should always be done with caution, our results indicate that this group is somehow overlooked and insufficiently risk stratified. One obvious reason for this relates to the use of albuminuria rather than eGFR in the clinic to identify persons at high risk for diabetic kidney disease with a recommendation to intensify glucose-, lipid-, and blood pressure–lowering treatment. For type 2 diabetes, the lower levels of blood pressure (and borderline lower levels of LDL cholesterol) may also contribute to a lower perceived cardiometabolic risk.

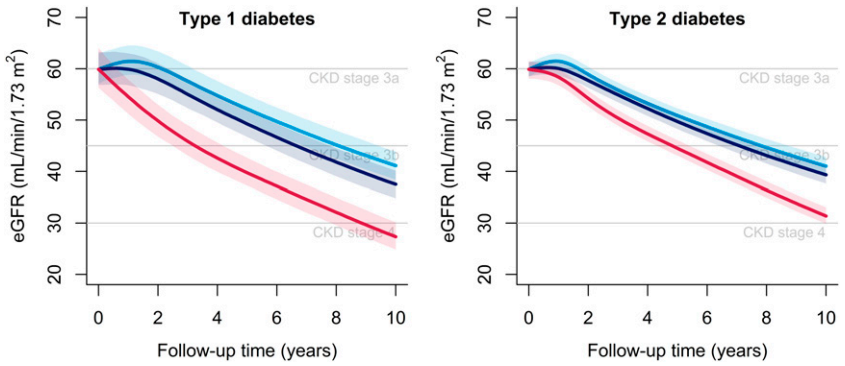

Figure 1—Estimated eGFR trajectories by diabetes type and albuminuria status for persons with a first recorded low eGFR just below 60 mL/min/1.73 m^2. Time 0 is the first clinical visit with a recorded low eGFR. Curves are shown for persons with normoalbuminuria (light blue), microalbuminuria (dark blue), or macroalbuminuria (red) with differences adjusted for sex, age at diabetes diagnosis, diabetes duration, calendar time, use of RAS blockers, retinopathy status, HbA_{1c}, antihypertensive treatment, blood pressure, current smoking, and lipid-lowering treatment. Solid lines are the estimated eGFR mean curves, and shaded areas are the corresponding 95% CIs. Horizontal gray lines show the thresholds for CKD stages.

In comparison with micro- or macroalbuminuria, normoalbuminuria was associated with a higher proportion of no retinopathy in both types of diabetes, possibly reflecting a harmless subtype of nephropathy caused by risk factors other than diabetes (5,6). However, we found no difference in the rate of eGFR decline between persons with and without any retinopathy ($P \geq 0.168$ [data not shown]). Among our study participants, 240 (7.8%) progressed to CKD stage 5 (CKD5), defined as eGFR <15 mL/min/1.73 m^2. While 81% had developed macroalbuminuria before CKD5, nearly one in five had not, suggesting that transition to macroalbuminuria is not a prerequisite for developing kidney failure defined by CKD5. There is ongoing discussion regarding the potential existence of a specific nonalbuminuric nephropathy phenotype in type 2 diabetes, but further exploration into structural differences would require a prospective renal biopsy cohort study combined with functional investigations to establish the existence of such a phenotype.

We found RAS blocking treatment to modify the eGFR decline in type 2 but not in type 1 diabetes. The randomized controlled trials showing benefits of RAS blocking treatment in type 2 diabetes have been conducted in high-risk populations with hypertension and macroalbuminuria, mostly using composite categorical outcome and not decline in kidney function over time (22). Studies are rarely long enough (>2 years of follow-up) to assess impact on eGFR, and so our study represents one of the few longtime assessments of the modifying effect of RAS blocking treatment. It is, however, important to remember that initiation of RAS blocking treatment may cause an acute decline in eGFR while subsequently stabilizing to a lesser rate of eGFR decline. Among our study participants with albuminuria, initiation of treatment with RAS blockers could have occurred prior to study baseline, which may explain the inability to demonstrate a clinically relevant effect of RAS blocking on eGFR decline in the current study.

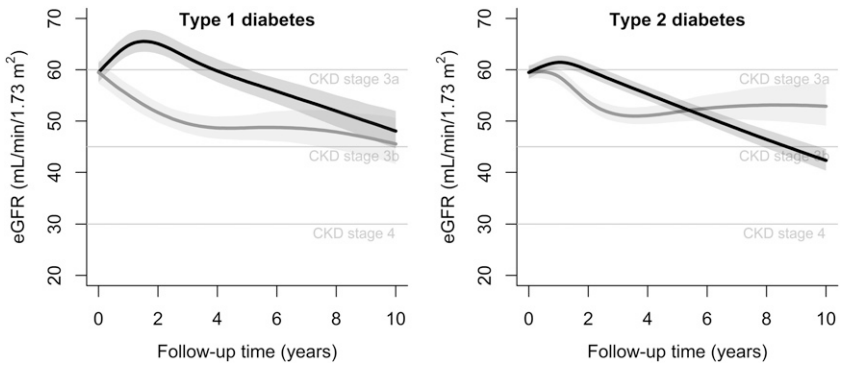

Figure 2—Estimated eGFR trajectories for the subset of persons with normoalbuminuria who were also without albuminuria at baseline for those with a first recorded low eGFR just below 60 mL/min/1.73 m^2. Time 0 is the first clinical visit with a recorded low eGFR. Curves are shown for the most frequent normoalbuminuric trajectory in black (86% and 90% for type 1 and 2 diabetes, respectively) and for the infrequent normoalbuminuric trajectory in gray (14% and 10% for type 1 and 2 diabetes) with differences adjusted for calendar time. Solid lines are the estimated eGFR mean curves, and shaded areas are the corresponding 95% CIs. Horizontal gray lines show the thresholds for CKD stages.

Clinical Perspective

In general, the annual age-related decline in eGFR from age 40 years is believed to be 1 mL/min/1.73 m^2 in the background population without CKD (23–25) down to 0.4 mL/min/1.73 m^2 in a healthy population of white ethnicity and without diabetes (26). The decline in persons with normoalbuminuria in our cohort is higher at ~1.9 mL/min/1.73 m^2 per year, most likely because CKD3 is reflecting some form of renal disease. Even after removal of eGFR measurements after periods with albuminuria in this subpopulation, the annual decline was still 1.4 mL/min/1.73 m^2 (data not shown). We have, however, not been able to investigate whether acute kidney injury preceded the development of CKD3. The proportion of normoalbuminuric participants with an early progressive eGFR decline was 14% in type 1 diabetes and 10% in type 2 diabetes (Fig. 2), which was somewhat higher than the 9% found in type 1 diabetes in the study by Perkins et al. (27). The higher proportion found in our study may be explained by the fact that participants with type 1 diabetes from the Joslin Diabetes Center were younger and healthier, including having much higher levels of eGFR at study entry. From a clinical perspective, it is comforting that most persons in a contemporary tertiary clinic preserve low annual decline in eGFR after development of CKD3. This is especially important in the groups with albuminuria, which had low annual decline (between 2.1 and 3.3 mL/min/1.73 m^2 per year) in eGFR compared with historical cohorts displaying much higher annual declines (~10–20 mL/min/1.73 m^2 per year) (28–30). In line with the improvements seen in eGFR

Table 3—Characteristics of the latent class trajectory classes by diabetes type at baseline

	Type 1 diabetes			Type 2 diabetes		
	Class 1	Class 2	*P*	Class 1	Class 2	*P*
N (%)	342 (86)	55 (14)		769 (90)	88 (10)	
No. of clinical measurements	5.0 (3; 9)	7.0 (4; 10)	0.021	5 (3; 8)	5 (3; 8)	0.762
Follow-up time (years)	5.3 (2.6; 9.1)	5.8 (3.2; 9.6)	0.640	4.1 (1.0; 6.8)	2.0 (0.8; 5.4)	0.027
Age (years)	65.0 (12.1)	66.8 (12.0)	0.297	69.8 (8.5)	73.9 (7.4)	<0.001
Male sex (%)	36.5 (31.4; 41.9)	34.5 (22.2; 48.6)	0.773	48.0 (44.4; 51.6)	39.8 (29.5; 50.8)	0.142
Age at diabetes diagnosis (years)	30.7 (15.2; 46.6)	32.3 (17.4; 40.0)	0.392	57.0 (49.4; 63.9)	59.9 (52.2; 69.7)	0.002
Diabetes duration (years)	31.9 (22.7; 43.2)	35.2 (25.8; 42.8)	0.597	12.7 (7.6; 18)	12.5 (5.7; 19.6)	0.706
HbA_{1c} (%)	8.4 (1.3)	8.6 (1.4)	0.352	8.1 (1.5)	7.7 (1.3)	0.059
HbA_{1c} (mmol/mol)	68.7 (13.7)	70.6 (15.7)	0.352	64.7 (16.8)	61.2 (14.8)	0.059
Height (cm)	169.7 (9.1)	170.8 (8.7)	0.408	169.4 (10.0)	167.8 (9.8)	0.155
BMI (kg/m^2)	25.5 (4.6)	25.3 (4.6)	0.718	30.4 (5.6)	30.6 (5.2)	0.781
eGFR ($mL/min/1.73\ m^2$)	55.6 (51.6; 58.1)	44.0 (35.4; 48.7)	<0.001	54.5 (49.1; 57.6)	33.9 (27.5; 39.5)	<0.001
UACR (mg/g)	8.0 (5.0; 16.0)	11.0 (6.0; 25.0)	0.031	8.0 (5.0; 17.0)	9.0 (5.0; 17.0)	0.821
Potassium (mmol/L)	4.3 (0.5)	4.3 (0.6)	0.466	4.3 (0.5)	4.4 (0.5)	0.013
Sodium (mmol/L)	138.4 (3.3)	138.1 (3.6)	0.644	139.2 (3.3)	139.6 (4.2)	0.313
Systolic blood pressure (mmHg)	137.3 (19.9)	142.6 (21.0)	0.074	136.9 (20.7)	131.5 (22.0)	0.021
Diastolic blood pressure (mmHg)	72.8 (10.4)	72.3 (10.1)	0.762	74.1 (11.1)	70.1 (12.5)	0.002
Total cholesterol (mmol/L)	5.0 (1.0)	5.4 (1.5)	0.011	4.6 (1.1)	4.5 (1.5)	0.336
HDL cholesterol (mmol/L)	1.8 (0.6)	1.6 (0.4)	0.009	1.3 (0.4)	1.2 (0.4)	0.055
LDL cholesterol (mmol/L)	2.6 (0.8)	3.1 (1.1)	<0.001	2.4 (1.0)	2.2 (1.0)	0.050
Triglycerides (mmol/L)	1.1 (0.8; 1.6)	1.3 (0.9; 1.8)	0.114	1.8 (1.3; 2.6)	1.9 (1.4; 2.9)	0.145
RAS blockers (%)	58.8 (53.4; 64.0)	67.3 (53.3; 79.3)	0.228	55.0 (51.4; 58.6)	42.0 (31.6; 53.0)	0.021
Antihypertensive treatment (%)	77.5 (72.7; 81.8)	85.5 (73.3; 93.5)	0.165	72.2 (68.9; 75.3)	56.8 (45.8; 67.3)	0.004
Lipid-lowering medication (%)	49.4 (44; 54.8)	34.5 (22.2; 48.6)	0.039	54.6 (51.0; 58.2)	39.8 (29.5; 50.8)	0.008
Retinopathy status (%)						
No apparent retinopathy	22.3 (17.7; 27.5)	7.3 (1.5; 19.9)	0.014	47.4 (43.6; 51.3)	47.0 (34.6; 59.7)	0.946
Mild/moderate retinopathy	29.7 (24.6; 35.2)	19.5 (8.8; 34.9)	0.162	24.3 (21.1; 27.7)	27.3 (17.0; 39.6)	0.596
Severe retinopathy	48.0 (42.2; 53.8)	73.2 (57.1; 85.8)	0.002	28.3 (24.9; 31.9)	25.8 (15.8; 38.0)	0.659
Smoking (%)						
No	61.8 (55.6; 67.7)	61.5 (40.6; 79.8)	0.981	65.0 (61.0; 68.9)	72.9 (59.7; 83.6)	0.219
Previous	3.5 (1.6; 6.5)	0.0 (0.0; 13.2)	0.186	3.7 (2.3; 5.5)	1.7 (0.0; 9.1)	0.391
Yes	34.7 (29.0; 40.9)	38.5 (20.2; 59.4)	0.707	31.3 (27.5; 35.3)	25.4 (15; 38.4)	0.344
Alcohol intake (units/week)*						
0	11.6 (8.0; 16.2)	4.3 (0.1; 21.9)	0.234	18.6 (15.5; 22.0)	19.6 (10.2; 32.4)	0.849
1–20	79.8 (74.4; 84.6)	91.3 (72.0; 98.9)	0.146	75.3 (71.5; 78.8)	78.6 (65.6; 88.4)	0.577
>20	8.5 (5.4; 12.6)	4.3 (0.1; 21.9)	0.448	6.1 (4.3; 8.4)	1.8 (0.0; 9.6)	0.125
Regular exercise (%)†	64.6 (58.4; 70.4)	54.2 (32.8; 74.4)	0.316	46.2 (42.1; 50.4)	25.9 (15.3; 39.0)	0.002

Data are mean (SD), median (interquartile limits), or proportion (95% CI). *P* is the level of significance for the unadjusted test of overall difference between classes, using *t* tests for difference in means or log(means) and χ^2 tests for difference in proportions. *A unit of alcohol: 12 g pure alcohol. †Regular exercise: ≥30 min per day.

decline, the incidence of ESKD in Danish persons has stabilized during recent years despite an increasing number of persons with diabetes (31).

Previous studies have demonstrated large variation in eGFR progression in persons with diabetes. Our study shows that this also applies after the manifestation of moderate loss of kidney function (CKD3), even among persons with normoalbuminuria, where some are already on an accelerated declining eGFR trajectory. It is important to identify these persons to prevent further loss of renal function and associated complications such as end-stage renal disease. Regular assessment of albuminuria and eGFR should therefore be performed as recommended in current guidelines (3), and ideally individualized risk assessment models should be developed.

Strengths and Limitations

A major strength of the study relates to the large single-center longitudinal data set with repeated detailed clinical measures and a follow-up of 16 years. This enabled us to account for change over time in covariates such as treatment and to relate trajectories of eGFR development according to degree of albuminuria for persons with diabetes entering CKD3. With the use of cubic splines to model development over time, we were further able to detect temporal changes in eGFR levels, such as the initial improvement we found in normoalbuminuria.

A single low eGFR was used as inclusion criteria in our study. Other studies have used sustained low eGFR (5,32) to increase the likelihood of the study

population being truly renal insufficient. We chose this approach to maximize power but mainly to facilitate the study of heterogeneity in eGFR development among persons with normoalbuminuria.

Typically, trajectories of eGFR have been investigated for the total group with normoalbuminuria, which may oversimplify the heterogeneous progression patterns preceding diabetic kidney disease. We used LCTM to find subgroups with distinct eGFR growth patterns among persons with normoalbuminuria. The LCTM approach has the advantage of being hypothesis free, thus enabling the identification of heterogeneity in eGFR development that would not be identified by use of conventional methods. One disadvantage of LCTM is, however, that some subgroups tend to be very small, potentially limiting statistical power as well as generalizability of the results. Furthermore, for the normoalbuminuric class 2 with progressive declining eGFR levels, follow-up time was short, and due to competing risk from mortality (33), the long-term trajectory of eGFR may reflect a healthy survivor bias. However, similar patterns have been found in a study of African Americans with multiple eGFR measurements over a median of 9 years of follow-up (8).

There are other study limitations. First, in around half of the clinical examinations, albuminuria status was based on a single spot urine from first morning void rather than on 24-h urinary albumin excretion. This could potentially have resulted in some misclassification (34). Second, glomerular filtration rate was estimated and not measured directly, which may involve some degree of imprecision to the trajectories. Third, while the population with type 1 diabetes is representative of the general Danish population with type 1 diabetes, the population with type 2 diabetes has relatively advanced disease and often significant late diabetes complications. The relatively advanced disease state in our population with type 2 diabetes may partly explain why we found a higher annual eGFR decline among those with normoalbuminuria than in a recent study on the younger and healthier Chronic Renal Insufficiency Cohort (CRIC), which showed a decline of only 0.17 mL/min/1.73 m^2 per year (35). Another factor that could explain the discrepancy is that the CRIC study used an internal glomerular filtration rate–estimating equation and eGFR levels up to 70 mL/min/1.73 m^2 were used as entry criteria in the younger age-groups (<45 years old). Lastly, because the population with diabetes in this study is predominantly of Danish ancestry (>90%), extrapolating results to nonwhite ethnicities should be done with caution.

Conclusion

Our results support a diabetes-dependent decline in kidney function without albuminuria following CKD3, and among these individuals, a subgroup shows a progressive decline. Furthermore, this group seems to be somehow undertreated in terms of cardioprotective and renal protective treatment, which suggests that increased attention should be drawn to normoalbuminuric diabetic kidney disease.

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Duality of Interest. D.V. and G.S.A. own shares in Novo Nordisk A/S. F.P. reports having received research grants from AstraZeneca and lecture fees from AstraZeneca, Merck Sharp & Dohme (MSD), Janssen, Eli Lilly, Boehringer Ingelheim, Novo Nordisk A/S, and Novartis, as well as being a consultant/advisory board member for AstraZeneca, Bayer, Amgen, and MSD. P.R. received lecture fees from Bayer and Boehringer Ingelheim and research grants from AstraZeneca and Novo Nordisk A/S and has served as a consultant for AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, AbbVie, and Novo Nordisk A/S (all honoraria to his institution). P.R. also owns shares in Novo Nordisk A/S. M.E.J. has received research grants from AstraZeneca, Amgen, Sanofi, and Boehringer Ingelheim (investigator-initiated research). M.E.J. also owns shares in Novo Nordisk A/S. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. D.V., F.P., P.R., and M.E.J. conceived of the study concept and design. D.V. and G.S.A. analyzed data. D.V., G.S.A., A.H., F.P., P.R., and M.E.J. took part in the interpretation of the results, commented on the manuscript, and had final responsibility for the decision to submit for publication. D.V. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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